a person of ordinary skill in the art "to use the device of Chang with sample volumes such that the amount of immobilized antibody was less than or equal to 0.1 V/K because this is less than the maximal amount of antibody Ekins '031 teaches may be employed to obtain volume independent results". Regarding claim 26, the Examiner maintains that the subject matter of claim 26 relates to "an optimization step within the level of skill of the ordinary artisan". The various subsidiary claims, 13-22, 24, 25, 27 and 28, stand rejected for the reasons set forth at pages 5 and 6 of the August 23, 1993 Official Action.

In accordance with the present amendment, claims 12, 23 and 26 have been amended by deleting the requirement that the binding agent is present at high coating density on the microspots. As disclosed in the paragraph bridging pages 11 and 12 of the present specification, it is not necessary for the binding agent to be present at high density, the improvement in sensitivity being achievable by the reduction of the size of the spot, rather than changing the coating density. Thus, the amendments presented herewith are not intended to be responsive to any ground of rejection set forth in the August 23, 1993 Official Action, but to eliminate from the claims what is considered an unnecessary limitation.

For the reasons set forth below, each of the objections and rejections set forth in the August 23, 1993 Official Action, which are addressed in turn in the following discussion, are respectfully traversed.

**A. The 35 U.S.C. §112, First Paragraph, Objection to Specification and Rejection of Claims 12-28**

It is well settled that when the adequacy of enablement provided in an applicant's specification is challenged, the PTO has the initial burden of giving reasons, supported by the record as a whole, why the specification is considered not enabling. In re Armbruster, 185 U.S.P.Q. 152

(CCPA 1975). In the present case, the Examiner has merely questioned the computation method employed by applicant in arriving at the values of 0.1 V/K set forth in the present specification. No reasoning or evidence has been presented to support the Examiner's position that those skilled in the art would not be able to practice applicant's invention based on information provided in the present specification. That being the case, the Examiner has not properly substantiated the §112, first paragraph, rejection based on alleged insufficiency of disclosure.

More specifically, the Examiner contends that the application is not enabling as regards the calculation of the amount of binding agent used in the present invention, namely, 0.1 V/K moles and 0.01 V/K moles, as the Examiner obtained different values of the number of molecules of binding agent compared with the disclosure on page 5 of the specification. The Examiner goes on to say that as the calculation of 0.1 V/K is essential to the present invention, it is necessary to establish where the specification teaches its proper calculation.

In reply to this, the applicant submits that, with the exception of claims 25 and 28, the claims are not limited to the number of molecules of binding agent, rather the number of moles of binding agent, see claims 12, 23 and 26. As the Examiner has himself demonstrated, it is straightforward for the person skilled in the art to calculate the number of moles of binding agent to conform with the 0.1 V/K criterion, knowing the volume of the sample and the equilibrium constant of the binding agent for the analyte. It is, therefore, submitted that the specification is enabling in this respect.

In fact, the source of the Examiner's objection appears to be that the passage on page 5 goes on to calculate approximate numbers of molecules of binding agent corresponding to 0.1 V/K and 0.01 V/K moles of binding agent. The amounts of binding agent located on the microspot were approximately expressed as numbers of molecules to give the

reader some sense of the order of magnitude of the numbers involved, and to warn against allowing the number to become so small that statistical variations in the number of occupied sites might affect precision and sensitivity.

Therefore, the skilled person could, if necessary (see below), calculate more exactly the numbers of molecules represented by the number of moles simply obtained by multiplying the number of moles by Avogadro's number, i.e., $6 \times 10^{23}$. However, the calculation on page 5 of the approximate number of molecules of binding agent corresponding to 0.1 V/K moles is made using an approximation of Avogadro's number, namely $10^{23}$. This is the source of the discrepancy between the Examiner's calculation and the calculation presented on page 5.

Thus, there is no dispute with the Examiner's more precise calculation; however, such a precise figure is not required for enablement. If it were true, there would be no difficulty in the skilled person employing the more precise value for Avogadro's number. For example, he might do so in order to know for the purposes of claims 25 and 28 whether he has more than $10^4$ molecules of binding agent. However, $10^4$ is only a preferred figure, as stated at page 5, lines 18 to 19 of the present specification.

It is, therefore, submitted that the number of molecules of binding agent is not only readily calculated, but is, as mentioned above, not an essential feature of the present invention, i.e., the present invention can, and normally will, be carried out without knowing or calculating the number of molecules of binding agent used. The present specification would have been fully enabling without any mention of numbers of molecules; this was added merely to explain in general, qualitative terms what is happening. Further, the passage referred to above does, however, note that the figures provided for the number of molecules immobilized at a location are approximate (see page 5, lines 4-5 of the present specification).

Similar comments apply to the Examiner's position regarding the adequacy of the disclosure relative to the figure of $10^4$ molecules. The actual disclosure in the application is given on page 5, lines 18-19: "practical considerations may give rise to a preference for more than $10^4$ molecules", i.e., this is a preference, not a necessity.

Although in theory it is not necessary for the assay to use more than $10^4$ molecules for it to function (i.e., this is not an essential feature of the invention), in practice it is found that when the number of molecules in a spot drops below $10^4$, statistical errors in counting the small numbers of occupied binding sites start to become significant. The person skilled in the art would realize that the use of low numbers of molecules of binding agent would make it more difficult to detect them when the fractional occupancy of the binding sites of the binding agent by analyte is measured. Quite simply, the person skilled in the art can decide for a given situation whether the statistical errors in using a given number of molecules are acceptable. Thus, by way of example, if 10,000 antibody molecules were located on a microspot, measurement of an analyte concentration resulting in an occupancy of 50% of the antibody sites would be subject to statistical error of 1.5%, an error that many analysts would find acceptable.

The important point is that the operation of the invention involves the calculation of the V/K ratio. These are macro-level values that are easily and routinely determinable. Calculation of the number of molecules is either not needed at all, or would be used as a kind of rough check to provide an indication of where the invention was operating in those embodiments where the amount of binding agent used is so small that statistical effects become noticeable.

Applicant's position that the disclosure of the present specification is sufficient to enable those skilled in the art to practice the claimed assay methodology is fully

supported by the Declaration of Dr. Johann Berger, which is submitted herewith. Dr. Berger's Declaration considers the objections raised by the Examiner in this connection and concludes, first of all, that the calculation of the appropriate number of moles of binding agent could easily be made by the person of ordinary skill in the art. (See paragraph 8 of the Declaration of Dr. Johann Berger). Dr. Berger further states in his Declaration that the applicant's specification makes clear that the subsequent calculation of the number of molecules of binding agent corresponding to the calculated molar amounts is merely an approximation and that the number of molecules of binding agent is not an essential feature of the invention, in any event. Regarding the reference to $10^4$ moles in applicant's specification, Dr. Berger states that this is a preferred aspect of the present invention and would be recognized as such by those skilled in the art.

In the absence of evidence or reasoning sufficient to meet the PTO's initial burden under 35 U.S.C. §112, first paragraph, the objection and related rejection based on 35 U.S.C. §112, first paragraph, as set forth in the August 23, 1993 Official Action, is clearly improper and should be withdrawn.

**B. <u>The 35 U.S.C. §103 Rejection of Claims 12-28</u>**

The Examiner has effectively acknowledged that the present invention is not anticipated by Ekins '031 and now argues that claims 12 to 28 are obvious in light of Ekins '031, considered together with Chang '570. The Examiner's position in this regard is vigorously disputed for the reasons that:

(1) Ekins does not teach the use 0.1 V/K moles of binding agent used in feature of the present invention;

(2) Chang does not disclose the features the Examiner argues are present in it, and in fact contains teachings diametrically opposed to Ekins; and

(3) Chang, therefore, does not combine with Ekins in the way the Examiner suggests. Ekins and Chang concern different types of assay and there would have been no incentive for the person of ordinary skill in the art to combine them, nor any way in which they can be easily combined.

**1. Ekins '031 Does Not Use Less Then 0.1 V/K Moles of Binding Agent**

As the Examiner notes, Ekins '031 concerns an assay methodology wherein results which are sample-volume independent are obtained using a small amount of binding agent that does not significantly alter the concentration of the analyte in the sample. In contrast to many people who are skilled in the art, the Examiner has appreciated that the error due to volume variation in this assay essentially becomes insignificant under these conditions.

However, Ekins '031 defines the amount of binding agent used operationally and does not define it in terms of physicochemical parameters (e.g., V,K) as in the present case. In order to make such a comparison, the Examiner calculates from the examples in Ekins '031 the amount of binding agent used in the samples having volumes 0.2, 0.4 and 0.8 ml. In fact, working out these figures provides amounts of binding agent equal to V/K, 0.5 V/K and 0.25 V/K, respectively. These amounts are all in considerable excess of the more stringent requirements of this application.

It would not have been obvious that any advantage can be obtained by reducing still further the amount of binding agent; after all, it would at first sight seem that this would result in a reduction in the signal obtained and make the assay less sensitive. However, as discussed below, the assay can in fact be just as sensitive at the levels of binding agent now claimed (0.1 V/K or even a great deal smaller).

One distinct advantage of the assay of the invention which is not disclosed or suggested in Ekins and which clearly is not obvious from Ekins '031 is that the use of an amount of binding agent less than 0.1 V/K moles results in a small amount of analyte being removed from the total, irrespective of analyte concentration (i.e., on the flat portions of the curves in the figure accompanying the present application).

This is certainly not the case in Ekins '031, which only requires the amount of binding agent not to significantly deplete the ambient concentration of analyte, i.e., the small amount of Ekins '031 has necessarily to be related to the expected analyte concentration. Ekins '031, therefore, has the disadvantage that the person carrying out an assay described therein has to know at least approximately the expected concentration of the analyte in the sample. This is a problem where the concentration of an analyte varies over a considerable range, i.e., the *in vitro* concentration of the hormone HCG varies from around 0.1 to 100 or more IU/ml, see page 10, lines 30 to 32 of the present application.

In the present invention, only the volume of the sample and the affinity constant of the binding agent need to be known to calculate a suitable amount of binding agent. As the Examiner will appreciate, this is an important practical advantage over Ekins '031.

Therefore, Ekins does not lead the person of ordinary skill towards the present invention and does not disclose the advantages of the claimed invention.

It has long been recognized that silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow. In re Burt, 148 U.S.P.Q. 548 (CCPA 1966).

**2. Chang Does Not Disclose the Features the Examiner Relies on in Rejecting Applicant's Claims**

**(a) The Assay of Chang is Qualitative, Not Quantitative**

Firstly, it must be pointed out that the assay of Chang is qualitative and provides no disclosure of deducing analyte concentration from the fractional occupancy of binding sites of the binding agent.

This can be seem from column 1, lines 54 to 56 where Chang talks about determining "the presence of particular antigens", and the fact that results from Chang are apparently determined visually, see column 6, lines 23 to 25.

In assessing Chang, the Examiner makes some calculations based on certain assumptions (e.g., adsorption conditions and affinity constants) to show that Chang is operating under the 0.1 V/K moles of binding agent required in the present invention. The Examiner's calculations are unsound, not because of the mathematics, but because they are based on certain incorrect or inappropriate assumptions (including the assumption that only a single binding site on the cell surface is bound to antibody on the spot). Thus, the conclusions the Examiner draws from Chang are, therefore, unfounded.

**(b) Chang Aims to Bind all the Analyte in the Sample**

Importantly, Chang uses antibody immobilized on a surface as a matrix of spots to bind red blood cells applied to the surface. The method disclosed in Chang aims to bind all the analyte present in the sample, filling each spot to maximum capacity; see column 6, lines 54 to 57 and Table 1 and column 7, lines 42 to 51. This approach is diametrically opposed to the techniques in Ekins '031 and the assay of the present invention wherein small amounts of binding agent are

used so that the ambient concentration of analyte in the sample is substantially unaffected.

**(c) Multiple Antibodies Bind to Single Red Blood Cells Greatly Increasing the Affinity Constant in Chang**

The cells bound in Chang would necessarily be bound to multiple antibodies via antigen present on their surface to achieve tight binding. This is even explicitly sought by Chang (see column 3, lines 16 to 19). Even if the assumptions the Examiner makes were true, which the applicant respectfully disputes, the fact that multiple antibodies are involved in binding means that the affinity constant is far larger than that used by the Examiner in his calculations. If two antibodies bind a cell, each having an affinity constant of $10^8$l/mol then the overall affinity constant is calculated by multiplying the individual affinity constants, i.e., it would be $10^{16}$l/mol. Further, it is likely that in Chang more than two antibodies would bind to a cell, and so this figure will probably be even higher still.

Clearly, therefore, Chang does not teach the use of 0.1 V/K moles of binding agent, as the binding of cells with such high affinity constants means that the amount of binding agent satisfying the 0.1 V/K moles requirement will be far lower than that actually used in Chang (as K increases, so the amount of binding agent satisfying 0.1 V/K moles is reduced). In other words, Chang uses a great deal more than 0.1 V/K moles of binding agent.

In summary, Chang discloses only a qualitative assay which aims to remove all the analyte from the sample (in the manner of prior art non-competitive assays) and which uses an amount of antibody well in excess of 0.1 V/K moles. This is diametrically opposed to the "ambient analyte" concept of Ekins '031, and does not combine with Ekins in any obvious fashion, and certainly not so as to lead the person of ordinary skill in the art to arrive at the assay of the

present invention. Neither reference suggests the advantages of such a combination nor enables the person skilled in the art to realize them in practice.

**3. Chang Represents an Assay Methodology Fundamentally Different From That of Ekins '031 and Thus Cannot Properly be Combined with Ekins '031 so as to Render the Present Invention Obvious**

As noted by the PTO Board of Appeals in Ex parte Wolters, 214 U.S.P.Q. 735 (Bd. Apps. 1979), the burden of establishing a *prima facie* case of obviousness falls upon the Examiner. In determining whether a case of *prima facie* obviousness exists, it is necessary to ascertain whether or not the disclosures of the cited prior art would appear to be sufficient to one of ordinary skill in the art to make the claimed substitution, combination or other modification. In re Lalu, 223 U.S.P.Q. 1257 (Fed. Cir. 1984). Merely because it is possible to find two prior art disclosures which might be combined in such a way as to arrive at the claimed subject matter does not make the combination of disclosures obvious unless the art also contains something to suggest the desirability of the proposed combination. In re Imperato, 179 U.S.P.Q. 730 (CCPA 1973).

In the present case, there is nothing to suggest the desirability of combining the disclosures of Ekins '031 and Chang in the manner proposed by the Examiner.

As mentioned above in 2.(b), the non-competitive assay disclosed in Chang seeks to bind all the analyte in a sample (as is conventional in the art - see below). To this end, an excess of binding agent is used an the analyte is bound by multiple binding agent molecules.

Prior art competitive assays were in general carried out according to the recommendations of Berson and Yalow; see the reference to their work on page 2, line 10 through page 3, line 33 of the present specification. Berson and Yalow

recommended the use of binding agent to bind 30-50% of the analyte in order to maximize the sensitivity of competitive assays (see page 4, line 26 of this application).

With the exception of Ekins '031 (see the discussion above), the above approach represents the paradigm accepted by most practitioners in the field right up to the present day. To exemplify the approach taken in the art for non-competitive assays, there is enclosed, as Exhibit A, for the Examiner's reference an article published in Clinical Chemistry, 37: 2002-2008 (1991) in which the American Thyroid Association (ATA) reviews assays for TSH, an analyte assayed for in Example 3 of the present application.

On page 2006, column 2, last paragraph, the ATA notes that non-competitive IMA assays use "much larger quantities of antisera because an excess of the first antisera is needed to bind the majority of the analyte in the sample" (emphasis added). This view plainly exemplifies the direction taken in the immunoassay field towards using excess amounts of binding agent in non-competitive assays.

In order to put the sensitivity of the assay of the present invention into context, the Examiner's attention is respectfully directed to the applicant's recent letter published in Clinical Chemistry, 39: 369-370 (1993), a copy of which is enclosed as Exhibit B. Exhibit B discloses a microspot assay for TSH which achieved a sensitivity of 0.0002 mU/l. The applicant's assay was also the subject of a slide at the recent interview on this case.

The Examiner will see from the last paragraph on page 2007 of Exhibit A that "the majority of commercially available TSH IMAs appear capable of distinguishing normal from hyperthyroid values in ambulatory patients but cannot reliably differentiate between the mildly subnormal values (0.01-0.1 milli-int unit/l) seen in hospitalized or $T_4$ treated patients . . ." Comparing these sensitivities, the Examiner will see that the assay disclosed in the present application is of the order of 50 to 500 times more sensitive than the

best of the assays of the prior art, and can determine concentrations of analyte where the prior art assays cannot even detect its presence.

It is, therefore, submitted that given the widespread practice in the field to adopt these approaches to competitive and non-competitive assays, the person of ordinary skill would not contemplate combining Ekins '031 with Chang (or other mainstream prior art) with any expectation of success, as the two methodologies represent contradictory approaches. The skilled person would, therefore, be prejudiced against combining the teachings of Chang with the quite different ideas contained in Ekins, given this prevailing view in the field, even if such a combination were in principle possible - which must be doubted for Chang at least.

In short, the approach of the applicant completely contradicts the design rules for immunoassays set out by practitioners in the art such as the American Thyroid Association and Berson and Yalow. The approach of the applicant was not obvious to some of those of exceptional skill in the art, let alone the person of ordinary skill. The applicant has spent considerable effort over the years trying to convince eminent practitioners in the field how reducing the amount of binding agent below 0.1V/K moles can provide a sensitive assay.

Inasmuch as the prior art references cited in support of the §103 rejection fail to teach or suggest the claimed subject matter as a whole, it necessarily follows that the prior art does not render applicant's invention *prima facie* obvious.

**(a) No Prior Art Teaches the Sensitivity Advantages Obtained Using Microspots of Immobilized Binding Agent**

The claims of the present application also require that binding agent is immobilized in small, spaced apart

spots. This maximizes signal-to-noise ratios, thereby improving the sensitivity of the assay. This is discussed at page 11, line 24 through page 12, line 12 of the present specification. Prior art such as Chang and Ekins '031 do not disclose this technical feature nor its advantage as regards sensitivity. Although the present invention represents a total departure from the conventional approaches relating to competitive and non-competitive assay designs taken respectively by Berson Yalow and the American Thyroid Association, the achievement of high sensitivity has been a principal object of immunoassay since the inception of this methodology. Given the desirability of this goal, if the present application were obvious in light of Ekins '031 and Chang, surely there would be some suggestion of doing this in the prior art.

As evidence of the pioneering work the present inventor has carried out, an editorial from Clinical Chemistry, 39: 1359-1360 (1993) is enclosed herewith as Exhibit C, which emphasizes the important contributions of the present inventor. See page 1359 column 1, paragraph 3.

**(b) Distinctions Regarding Applicant's Dependent Claims**

The foregoing comments distinguish the independent method, device and kit claims (claims 12, 23 and 26) from the prior art as these claims all contain the requirement that less than 0.1 V/K moles of binding agent are present in microspots on a support. If these claims are allowable, then the dependent claims the Examiner discusses on pages 5 to 7 of the Official Action are also clearly allowable. Nevertheless, comment regarding the statements made by the Examiner in support of the rejections of these claims is believed to be in order.

The Examiner comments on claims 13 and 14 that it would be obvious that decreasing the spot size would increase the signal-to-noise ratio and give greater sensitivity.

However, the Examiner may have been thinking in terms of decreasing the spot size for a given amount of binding agent, thus increasing the density of the binding agent. The Examiner may thereby not have appreciated that the effect is obtained by decreasing the spot size for a given density of binding agent, i.e., the density of binding agent can remain the same, the amount of binding agent is thereby reduced, and yet still the sensitivity increases (to a plateau) as the spot gets smaller. Thus, it is respectfully submitted that the person of ordinary skill in the art would approach the problem in the way the Examiner suggests and not appreciate the above-noted distinction. Furthermore, implicit in the Examiner's position in this regard is that all kit manufacturers and other workers skilled in the art who have previously attempted to increase the amount of capture antibody in a non-competitive assay (by increasing the surface area of the solid supports on which such antibodies have been deposited) to increase sensitivity have been doing something which is obviously incorrect. Such a position plainly cannot be sustained.

It will thus be recognized from the foregoing discussion that a greater sensitivity can be achieved by reducing the amount of binding agent below 0.1 V/K. It is believed that, upon reflection, the Examiner will appreciate that this would have been counter-intuitive to one of ordinary skill in the art.

Although Chang purports to disclose spots of 1 $mm^2$ or less, it neither appreciates nor teaches the concept of the present invention. In this regard, the Examiner's attention is respectfully directed to the accompanying figure (Exhibit D, which was referred to at the recent interview) which shows the effect of coating the binding agent on a solid support at constant density on smaller and smaller areas. Contrary to the accepted rules of assay design, which emphasize that maximum sensitivity is achieved using large amounts of binding agent, the sensitivity of the assays of the present invention

increases as spot size is reduced. It is submitted that this is a surprising result that would not have been apparent to the person skilled in the art.

Claims 14 and 25 concern the use of more than $10^4$ molecules of binding agent. Basically, the use of more than $10^4$ molecules is preferred for practical reasons relating to statistical errors in counting such small amounts of binding agent. However, this is not an essential feature of the present invention and has been commented on above in addressing the enablement issue.

The 0.01V/K of binding agent required by claim 15 is a preferred feature of the present invention and is not essential to carrying out the applicant's assay. In any event, as discussed above, the device of Chang does not use small amounts of binding agent below 0.1 V/K moles.

**4. The Berger Declaration Substantiates the Non-Obviousness of Applicant's Assay Method**

The aforementioned Declaration of Dr. Johann Berger also supports applicant's position that the assay methodology of claims 12-28 is patentable over the combined disclosures of Ekins '031 and Chang. In his Declaration, Dr. Berger, who has over twelve years of experience in the diagnostics field, not only confirms the existence of patentable distinctions between the present invention and the disclosures of Ekins '031 and Chang, but also establishes the commercial significance of the present invention.

Dr. Berger reviews the amounts of binding agent actually used in the assay described in Ekins '031, and points out that the disclosed amounts are all in considerable excess of the amount of binding agent required in the practice of the present invention, namely, 0.1 V/K. Dr. Berger considers this aspect of applicant's invention to be unobvious because it runs counter to the accepted practice in the field of using large amounts of binding agent to obtain optimal sensitivity. Furthermore, Dr. Berger considers the increased sensitivity

provided by the claimed assay method as the size of the spot containing binding agent is reduced to be a surprising result. Dr. Berger also comments on a further practical advantage of the present invention in that by using 0.1 V/K moles of binding agent only a small amount of analyte is removed from the total, irrespective of the analyte concentration. As noted by Dr. Berger, this is particularly beneficial where the expected concentration of an analyte varies over a large range, and is not suggested by Ekins '031.

Dr. Berger's Declaration also concurs with applicant's position regarding the lack of relevance of Chang. As noted by Dr. Berger, Chang uses an amount of binding agent much greater than 0.1 V/K moles, which he considers not surprising as the assay of Chang conforms to the accepted practice of using large amounts of binding agent in order to achieve high levels of analyte binding, so as to maximize sensitivity.

Dr. Berger's Declaration also speaks to the commercial significance of the present invention. As stated in paragraph 4 of Dr. Berger's Declaration:

> It was our assessment that Professor Ekins' pioneering work had opened up an entire new approach in this field, allowing multi-analyte, miniaturised assays to be developed, which could be the basis for a new generation of assays, and that my company would have an excellent commercial opportunity if it developed them. We therefore negotiated an exclusive license under all of Professor Ekins' patents and patent applications relating to the ambient analyte technology. At present, we are working on the commercial development of these assays and expect these to have important products on the market in the near future.

The profit motive in business being what it is, Boehringer Mannheim GmbH would not have obligated itself to pay licensing fees based on the present application if the assay methods and devices of this invention were merely an

obvious modification or variation of preexisting immunoassay design concepts.

The Declaration of Dr. Johann Berger, submitted herewith as Exhibit E, is a copy of a facsimile bearing Dr. Berger's signature. The original of Dr. Berger's Declaration will be submitted as a supplemental response to the August 23, 1993 Official Action.

In conclusion, it is respectfully submitted that the Examiner has not shown that the prior art discloses or points towards the use of 0.1 V/K moles of binding agent, nor the important practical advantages this approach has in assay performance.

For all of the foregoing reasons, it is respectfully urged that the objections and rejections set forth in the August 23, 1993 Official Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,

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- Exhibit A: Clinical Chemistry, 37: 2002-2008 (1991)
- Exhibit B: Clinical Chemistry, 39: 369-370 (1993)
- Exhibit C: Clinical Chemistry, 39: 1359-1360 (1993)
- Exhibit D: Figure
- Declaration of Dr. Johann Berger

U.S. Serial No. 07/984,264 Examiner: M. Woodward

Filed: December 1, 1992 Group Art Unit: 1813

**SCHEDULE A**
**CLAIM AMENDMENTS**

Claim 12, lines 9 and 10, delete "each spot has a high coating density of one of said binding agents but";

Claim 23, line 4, delete "at high coating density"; and

Claim 26, lines 4 and 5, delete "at high coating density".